REMARKS/ARGUMENTS

The application was filed with claims 1-53. Claims 4-5, 11, 14-16, 30-31, 37-38, and 41-43 have been canceled herein. No new claims have been added herein. Therefore, claims 1-3, 6-10, 12-13, 17-29, 32-36, 39-40, and 44-53 are currently pending. Claims 1, 13, 17, 19, 24, 27, 40, 44, 46, and 51 have been amended herein.

Information Disclosure Statements

Applicants appreciate the Examiner's acknowledgement of consideration of references A1-A148 and B1 submitted in Information Disclosure Statements dated October 29, 2004 and March 8, 2005, respectively. Applicants note, however, that the Examiner has not yet acknowledged consideration of references C1-C3, which were submitted in an Information Disclosure Statement dated September 12, 2005. Submission of references C1-C3 is believed to have been filed in a timely manner, because each item of information contained in the Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Information Disclosure Statement or was first brought to the attention of Applicants as a results of such communication and was unknown to Applicants more than three months prior to the filing of the Information Disclosure Statement. Consideration and acknowledgement of same is respectfully requested.

Furthermore, Applicants submit herewith a Supplemental Information Disclosure Statement and request consideration thereof.

No fee is believed due for consideration of references C1-C3, but enclosed herewith is payment including the fee of $180.00 for consideration of the Supplemental Information Disclosure Statement enclosed herewith. If, however, Applicants are incorrect, the Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 14-0629.

Claim Amendments

Claims 1 and 27 have been amended herein to delete one sub-genus of the Ar_2 rings disclosed in the original Markush groups. None of the remaining sub-genera of Ar_2 rings recited in those

claims have been amended or narrowed in any way. No new matter has been added by this amendment. Support can be found throughout the specification and specifically at, *inter alia*, claims 1 and 27, as filed.

Claims 13 and 40 have been amended to recite "breast cancer" rather than recite "uncontrolled cellular proliferation." Support for this amendment can be found at, for example, page 88, example 23.

Claims 17 and 44 have been amended to correct antecedency in view of the cancellation of claims herein.

Claims 19 and 46 have been amended herein to correct the spelling of "hypercholesterolemia." No new matter has been added by this amendment.

Claims 24 and 51 have been amended herein to delete the redundant word "to." No new matter has been added by this amendment.

Rejection under 35 U.S.C. § 102(b)

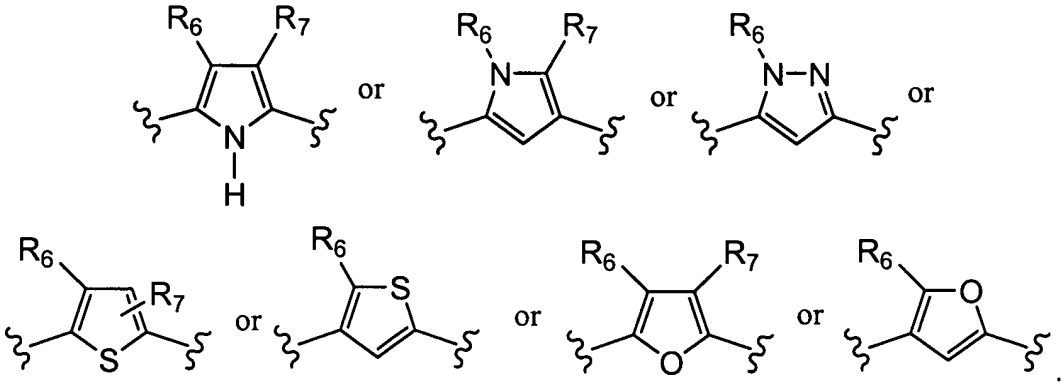
The Office Action has rejected claims 1-53 as anticipated by United States Patent No. 6,515,003 to Pfahl *et al.* (hereinafter Pfahl). The Office Action made a conclusory assertion that "Pfahl et al teach heterocyclic substituted thiazoline compounds and their use as recited in applicants' claims corresponding to the formula in claim 1. See for example, columns 1-3 and claims 1 and 15." Applicants respectfully disagree, as this conclusory assertion is not only factually erroneous; it is legally insufficient to support a valid prima facie rejection for anticipation.

To anticipate a claim under 35 U.S.C. §102(b), each and every element of the claim must be disclosed in the cited reference. The Office Action has failed to address MANY specific structural features of the Ar_1 and Ar_2 groups recited in the chemical drawings in Applicants' independent claims 1 and 27, and has certainly failed to support a claim that each of those structural features is disclosed in Pfahl.

For example, the bicyclic Ar_1 rings recited in claim 1 have saturated six membered rings comprising oxygen atoms and R_1-R_4 groups at specific positions within the overall bicyclic ring

structure, in combination with specifically recited selections of R_1-R_4 groups. In order to properly support a valid *prima facie* rejection for anticipation, the Office has the legal burden to specifically identify in Pfahl each of the particular structural features illustrated in the drawings of the Ar1 rings, a burden that the Office action simply failed address. Such an assertion is simply erroneous as a matter of fact, because nowhere does Pfahl recite the combination of structural features of the Ar_1 rings of Applicants independent claims 1 and 27.

Amended independent claims 1 and 27 also recite, Ar_2 rings having the structure:



Pfahl does not disclose compounds wherein Ar_2 is one of the above structures comprising five-membered heterocyclic rings. Therefore Pfahl does not anticipate amended independent claims 1 and 27. Consequently, Pfahl cannot anticipate the pending claims. Therefore, this rejection has been overcome.

Rejection under 35 U.S.C. § 103(a)

The Office Action rejected claims 1-53 as obvious in view of Pfahl. As justification for the asserted rejection, the Office Action states:

> Pfahl et al differs in the heterocyclic linking group employed between the bicyclic and thaizoline moiety. However, in view of the art as a whole and the close structural relationship between the compounds and linking groups as a whole it would have been obvious to one of ordinary skill in the art to modify Pfahl et al to employ other analogous heterocyclic linking groups as the use of somewhat different but other analogous groups would not have been unexpected and therefore unpatentable.

Office Action mailed September 26, 2005 at page 3.

Applicants respectfully disagree that the pending claims are obvious. It is the burden of the Office to show that the prior art, when considered as a whole, teaches or suggests every element of Applicants' claims. Moreover, "There must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *In re Kotzab*, 217 F.3d 1365, 1370 (Fed Cir. 2000). The suggestion or motivation asserted must also be supported by objective evidence, not mere conclusory assertions. *See In re Dembiczak*, 175 F.3d 994, 999 (Fed Cir. 1999). The prior art must also provide a reasonable expectation of success for the proposed combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed Cir. 1988). The asserted combination or modification must teach or suggest all claim limitations. *In re Royka,* 180 USPQ 580 (C.C.P.A. 1970) (stating that all claim limitations must be taught or suggested by the prior art). Thus, in order to establish a *prima facie* case of obviousness, the Examiner must show that 1) there is some suggestion or motivation in the reference or in the general knowledge of the art to combine or modify the references, 2) there must be a reasonable chance of success, and 3) the prior art must teach or suggest all the limitations of the claim. Applicants respectfully assert that this burden has not been met.

First, as noted above in Applicants' discussion of the anticipation rejections, the Office Action failed to address, let alone carry its legal burden to establish and support with evidence from the prior art that Pfahl teaches or discloses each and every one of the specific structural features recited in the structural drawings of the Ar_1 and Ar_2 rings of Applicants claims.

Specifically, Pfahl nowhere teaches or suggests either the use of the particular combinations of structural features of the Ar_1 ring, or the five-membered heterocyclic Ar_2 rings. In particular, there is absolutely no disclosure of pyrrole, imidazole, thiophene, or furan resdiues in Pfahl. Further, Pfahl does not teach or suggest the particular arrangement of substituents on the five-membered heterocyclics claimed in the instant application. Even if Pfahl had taught or suggested five-membered heterocyclic linking moieties, *which it did not*, Pfahl nowhere suggests that the use of the individual structural moieties is desirable, let alone their combinations or the necessary structural modifications.

Moreover, the cited reference must also suggest the desirability of the necessary modifications. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). Here, Pfahl does not provide any such suggestion.

Failing to find suggestion to make the asserted modification in Pfahl, the Office Action looks to "the art as a whole" for the requisite motivation. While logic and sound scientific principles may be relied upon in support of a rejection under §103, the Office Action must provide some evidentiary basis for the existence and meaning of the scientific principle relied upon. *See In re Grose*, 592 F.2d 1161, 1167-68 (CCPA 1979). Here, the Office Action has offered only a vague allegation of "close structural relationship between the compounds and linking groups." In fact, many individual structural and chemical modifications would be necessary to transform the compounds disclosed in Pfahl into the claimed compounds. To cite merely one example, the claimed heterocycles comprise five-membered Ar_2 rings, while the linkers of Pfahl are six-membered rings. Thus, among many needed modifications, to arrive at the claimed heterocyclics, one or ordinary skill must be motivated to alter the disclosed ring size. At least several of the necessary individual modifications cannot be found and are not motivated by Pfahl. Moreover, none of the multiple necessary modifications can be properly supported by a mere reference to "the art as a whole," as it is the legal burden of the office to support any such contention with specific evidence. Therefore, the assertion that "it would have been obvious to one of ordinary skill in the art to modify Pfahl et al to employ other analogous heterocyclic linking groups" is merely a conclusory statement that insufficiently supported by any specific reasoning or specific evidence. Such conclusory statements cannot support a proper *prima facie* rejection for obviousness.

At best, unsupported reference to "the art as a whole" might provide some evidence that it would be obvious to try other heterocyclic linking groups; however, neither Pfahl nor the Office Action provides any support for reasonable chance of success. And, as noted in MPEP § 2145, "obvious to try" is an improper standard under 35 USC § 103. This case is analogous to the situation described by the *In re O'Farrell* court. Specifically, the court stated that:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

In this case, the Office Action has completely failed to address or merely vaguely alluded to the requisite specific structural modifications and motivations therefore, and provided no specific or substantive evidence of a motivation for the necessary modifications, and therefore clearly engaged in impermissible hindsight reconstruction of the claimed invention.

Accordingly, the Office Action failed to sufficiently support a legally valid prima facie rejection for obviousness, and therefore failed to carry its burden of proof, and the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The Office Action did not reject original compound and composition claims 1-12 and 27-39 under 35 U.S.C. § 112, first paragraph. While Applicants have amended and/or cancelled some of those claims, amended compound and composition claims 1-3, 7-10, 12, 27-29, 32-36, and 39 remain pending and have not been rejected under 35 U.S.C. § 112, first paragraph.

The Office Action rejected original method of treatment claims 13-26 and 40-53 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The stated rejections are predominantly related to assertions that Applicants had not sufficiently enabled and/or supported with examples methods of treating a broad range of diseases of uncontrolled proliferation and/or various forms of cancer.

While not conceding the validity or the reasoning behind the rejections (as further discussed below), in the interests of facilitating prosecution to allowance, applicants have amended claims 13 and 40 to recite the treatment of breast cancer, a disease for which Applicants specification,

examples, and Figures do provide evidence of biological effectiveness. Claims 14-16 and 41-43, which originally related to treatment of other forms of cancer and/or diseases of uncontrolled proliferation, have been canceled (without prejudice or disclaimer thereof). Applicants specifically retain, and have not canceled claims 18-26, and 45-53, which relate to treatment of metabolic diseases of diabetes, and related diseases of carbohydrate and/or lipid metabolism, for which Applicants' specification provides evidence of relevant biological activity.

In view of Applicants continued pursuit of dependent method of treatment claims, Applicants hereby respectfully contest much of the reasoning underlying the original rejection of the original method of treatment claims. First, the Office Action rejections, which are completely devoid of specific evidence to support their assertions, are merely based on overbroad and poorly supported generalizations about the state of the art. Such generalizations, standing alone, cannot shift the legal burden of proof from the Office to the Applicant.

As the courts have stated, "[A]s a matter of Patent Office practice . . . a specification . . . must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). More specifically,

> [I]t is incumbent upon the Patent Office, whenever [an enablement] rejection is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224.

The Office Action did not provide legally "acceptable evidence or reasoning" to support its rejections, but only much less. For example, on pages 4-5, the Office Action offers conclusory assertions that

> The state of the prior art is that involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e.

> what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

These assertions of the Office Action conflict dramatically with the relevant law of the Federal Circuit, which states that "[t]he purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles, 628 F.2d at 1327, 206 U.S.P.Q. (BNA) at 890.* Modern science has previously identified numerous successful chemotherapeutic agents." *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

In view of the statements of the Federal Circuit, it is evident that the Office Action, rather than attempting to meet its own legal burden, instead attempted to improperly impose an improperly high burden of proof on Applicants. In a similar attempt to improperly shift the burden of proof to Applicants, the Office Action stated that "[i]t is not clear that that the assays correlate to any form of cancer. There is no evidence of functional treatment, i.e. no correlation to treatment in humans." In contrast, the *Brana* court stated that

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.

Applicants have provided data evidencing effectiveness in the treatment of breast cancer in human cell lines (Figure 5), and well accepted animal models (Figure 6). Applicants have also provided data evidencing effectiveness in treating metabolic diseases in Figures 1-4, in both recognized cell lines and recognized animal models. Under the law, nothing further is required of Applicants.

In yet another attempt to impose a legally improper burden on Applicants, on page 6, in connection with claims 18 and 45 relating to the modulation of carbohydrate and lipid metabolism, the Office Action objected that "it is not clear whether the desired effect is gained by modulating lipid metabolism up to modulating lipid metabolism down." First, Applicants

deny that they have any legal duty at all to state or clarify whether the modulation is "up" or "down." Applicants further note that their Figures 4a and 4b illustrate examples from recognized animal models of diabetic conditions wherein the compounds simultaneously beneficially modulate the concentration of undesirable HDL lipids "down," and beneficially modulate the concentration of desirable LDL lipids "up." Accordingly, it is both scientifically unreasonable and legally improper that the Office Action attempt to require Applicants to amend their claims to choose between "up" and "down."

Lastly, the Office Action made erroneous grounds of rejection. For example, the Office Action asserted on page 7 that "[t]he instant method of treatment/inhibition of cancer with additional anticancer agents as recited in the claims encompasses such unidentified anticancer agents, a description of which is not found in the specification." Applicants reply that on page 42 of the specification applicants described the use of the compounds of the invention with "another known and/or presently used anti-cancer agent." Applicants have no legal duty whatsoever to enumerate every known anti-cancer agent, but include on page 42 an exemplary list that includes Tamoxifen, Taxol, Taxol derivatives, Doxorubicin, and Cisplatin. Figure 6 illustrates the unexpectedly synergistic effect of the use of Applicants compounds in combination with Tamoxifen. Clearly, the assertion of the Office Action was factually incorrect.

Applicants believe this rejection to be overcome and respectfully request its withdrawal.

CONCLUSION

In light of the above arguments and amendments, the claims are believed to be allowable, and Applicants respectfully request notification of same. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issuance.

Payment in the amount of $630.00, including $180.00 for the Supplemental Information Disclosure Statement, and $450.00 for the Two-Month Extension of Time is enclosed herewith. The payment is to be charged to a credit card and is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. No further fee is believed due. However, the

Commissioner is hereby authorized to charge any fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Mark A. Murphy, Ph.D. — Date: Feb 27, 2006